

### PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 030811woMetg International application No. PCT/EP 03/04058			FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)			
			International filing date (day/mon	nth/year) Priority date (day/month/year)		
			17.04.2003	18.04.2002		
C12Q1	1/68 t	JROSCIENCES GMB	both national classification and IPC			
<del></del> :						
1. Th	is interi thority :	national preliminary exar and is transmitted to the	mination report has been prepar applicant according to Article 3	red by this international Preliminary Examining 6.		
2. Thi	is REP(	ORT consists of a total of	of 7 sheets, including this cover	sheet.		
Ø			nled by ANNEXES, i.e. sheets of pasis for this report and/or sheet 607 of the Administrative Instru	f the description, claims and/or drawings which is containing rectifications made before this Authorisms under the PCT)	have nority	
The		exes consist of a total o		such and the POT).		
3. This	s report	contains Indications rela	ating to the following Items:			
ŧ	$\boxtimes$	Basis of the opinion				
IJ		Priority				
111		Non-establishment of o	pinion with regard to novelty, inv	entive step and industrial applicability		
IV		Lack of unity of inventio				
V	Ø	Reasoned statement un	der Rule 66.2(a)(ii) with regard ns supporting such statement	to novelty, inventive step or industrial applicabil	ity;	
VI	_	Certain documents cited				
VII	_	Certain defects in the In				
			the international application			
ate of sub	mission	of the demand	Date of co	empletion of this report		
			3200,00	in plant of the report		
2.11.200	03		09.07.20	004		
ame and n eliminary e	examinir	ddress of the International ig authority: ean Patent Office - P.B. 56		1 Officer	Tari.c	
<u>an</u>	NL-22	80 HV Rijswijk - Pays Bas	Aquilera	, M	) j	
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J.	Basis	of the	report
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1. With regard to the elements of the international application (Replacement sheets which have been furnished the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	De	scription, Pages					
	1-3	14	as originally filed				
	Cle	aims, Numbers					
		i.					
	1-2	20	received on 06.05.2004 with letter of 06.05.2004				
Drawings, Sheets							
	1/1	0-10/10	as originally filed				
2.	Wit lan	h regard to the <b>lang</b> u guage in which the in	lage, all the elements marked above were available or furnished to this Authority in the ternational application was filed, unless otherwise indicated under this item.				
	The	ese elements were av	vailable or furnished to this Authority In the following language: , which is:				
		the language of a tr	anslation furnished for the purposes of the international search (under Rule 23.1(b)).				
		the language of pub	lication of the international application (under Rule 48.3(b)).				
the language of a translation furnished for the purposes of international preliminary examinable 55.2 and/or 55.3).							
3.	Wit	h regard to any <b>nucle</b> rnational preliminary	eotide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing:				
		contained in the inte	rnational application in written form.				
		filed together with th	e international application in computer readable form.				
	⊠.	furnished subseque	ntly to this Authority in written form.				
	$\boxtimes$	furnished subsequer	ntly to this Authority in computer readable form.				
	×	The statement that t in the international a	he subsequently furnished written sequence listing does not go beyond the disclosure pplication as filed has been furnished.				
The statement that the information recorded in computer readable form is identical to the writte listing has been furnished.							
J.	The	jamendments have r	esulted in the cancellation of:				
		the description,	pages:				
		the claims,	Nos.:				
		the drawings,	sheets:				
			·				

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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;	5. 🗀	This report has been estable been considered to go be	ablished eyond the	as if (some e disclosure	of) the amendments had not been made, since they have as filed (Rule 70.2(c)).	/e	
		(Any replacement sheet on report.)	containin	ng such ame	andments must be referred to under item 1 and annexed	to	
6	6. A	dditional observations, if neo					
1	íl. No	on-establishment of opinion	on with i	regard to no	ovelty, inventive step and industrial applicability		
1	ı. Th	ears to be novel, to involve an inventive step (to be non- been examined in respect of:					
		the entire international ap	plication	ı			
	$\boxtimes$	claims Nos. 9,10,12, 16-1	9				
		because:					
		the said international appli not require an internationa	cation, o	or the said cl nary examin	laims Nos. relate to the following subject matter which do	08	
the description, claims or drawings (indicate particular elenthat no meaningful opinion could be formed (specify):				articular elements below) or said claims Nos. are so uncl pecify):	lea		
		the claims, or said claims l could be formed.	Nos. are	so inadequa	ately supported by the description that no meaningful op	· <b>in</b> i	
	$\boxtimes$	no international search rep	ort has I	peen establi:	shed for the said claims Nos. 9,10,12, 16-19		
2.	Or E	A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:					
the written form has not been furnished or does not comply with the Standard.					e not comply with the Standard.		
		the computer readable form	n has no	t been furnis	shed or does not comply with the Standard.		
V.	. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicabilit citations and explanations supporting such statement						
1.	Stat	ement					
	Nov	elty (N)	Yes: No:	Claims Claims	1-8, 11, 13-15 and 20		
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-8, 11, 13-15 and 20		
	Indu	stnal applicability (IA)	Yes: No:	Claims Claims	1-8, 11, 13-15 and 20		
2.	Citat	ions and explanations			•		

see separate sheet

#### V. Reasoned statement (Continuation)

#### 2.1 CITATIONS

Reference is made to the following documents:

- D1: WO 00 55318 A (UNIV BRITISH COLUMBIA ;XENON BIORESEARCH INC (CA)) 21 September 2000
- D2: US-B1-6 225 525 (LEUNG WAI-PING ET AL) 1 May 2001
- D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2001 (2001-07), VAISMAN BORIS L ET AL: 'ABCA1 overexpression leads to hyperalphalipoproteinemia and increased biliary cholesterol excretion in transgenic mice.' XP002237202 Database accession no. PREV200100378305 & JOURNAL OF CLINICAL INVESTIGATION, vol. 108, no. 2, July 2001 (2001-07), pages 303-309.
- D4: US 2002 037843 A1 (LAM FRED CHIU-LAI ET AL) 28 March 2002

#### 2.2 NOVELTY (Art. 33(2) PCT)

- 2.2.1 D1 discloses methods and products for the diagnosis of neurodegenerative diseases, including Alzheimer's disease (see pages 46 to 51). It is explained that ABCA1 may act as a transporter of APP products out of cells, and therefore be useful in the context of amyloidosis. It is explicitly disclosed that down-regulation of ABCA1 may lead to decreased apoptosis in neurodegenerative disorders (see page 46, lines 22-25).
- 2.2.2 In particular, D1 describes a method of diagnosing a neurodegenerative disease by determining the level and/or activity of an ABCA1 gene product. Antibodies against ABCA1 can be used in the development of diagnostic assays by monitoring the expression or biological activity of ABCA1 (see page 48, lines 18-27). Other tools can be used to monitor said expression, for example RT-PCR (see page 49, line 9). It is also described a method of evaluating a treatment by measuring the levels of expression of an ABCA1 gene product (see page 49, lines 15-24). Therefore, the methods of claims 1-7 and 20 are not new.
- 2.2.3 The fact that D1 deals as well with other types of ABCA-1 related diseases is not relevant for the question of novelty, since the passages cited above are explicitly directed to neurodegenerative diseases, including Alzheimer's disease (see for

example page 46, line 6; or claim 34). Nevertheless, it must be noted that the reference to neurodegenerative diseases in the present claims is not restricted to Alzheimer's disease.

- 2.2.4 The kit of present claim 8 is not new because its single component, a reagent "that selectively detects a transcription product of the ABCA1 gene", was known at the time of filing. Any polynucleotide comprising any fragment of the ABCA1 gene falls under the scope of such definition, and examples can be found in D2 and D3, among others. The features characterizing the method in which the kit is to be used ("by detecting [...] health status") represent merely an indication of intended use in the context of a product claim. This IPEA considers the use of the product as an optional feature not limiting the scope of a product claim. Therefore, claim 8 is not new.
- 2.2.5 D2 discloses a recombinant non-human animal comprising a non-native gene sequence coding for ABCA1 which is *obtainable by* the process described in claim 11 (see Abstract and Figure 1). Therefore, claim 11 is not new. The fact that the recombinant animal is used as a model for other purposes is irrelevant to the question of novelty of a product claim (see above).
- 2.2.6 D1 discloses drug screens for modulators of neurodegenerative diseases, including Alzheimer's disease. The methods are based on the modulation of expression levels of ABCA1 gene products (see page 47, line 5, to page 48, line 17; claim 34), not only in cells (see page 54), but also in test animals (see page 59). Therefore, the methods of claims 13-15 are not new.
- 2.2.7 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-8, 11, 13-15 and 20 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

- 2.3 <u>SUFFICIENCY OF DISCLOSURE, CLARITY AND SUPPORT</u> (Arts. 5 and 6 PCT)
- 2.3.1 Article 6 PCT requires that the matter for which protection is sought be defined in the claims in a clear and concise manner, and that all the claims be supported by the description. The support by the description must be sufficiently clear for the skilled person to put the invention as claimed into practice without undue burden, i.e. no more than a reasonable amount of experimentation, and without applying inventive skill.
- 2.3.2 The current application documents demonstrate that ABCA1 mRNA is underexpressed in the post-mortem frontal cortex of Alzheimer patients, when compared to its expression in the post-mortem temporal cortex of the same patients. However, the scope of the subject-matter claimed covers the prognosis, diagnosis, monitoring and evaluation of any neurodegenerative disease by measuring the levels or activities of any genetic product of the ABCA1 gene. The discrepance between the claimed scope of protection and the actual teaching of the description is evidenced by the following:
- 2.3.2.1 The fact that any translation product of the ABCA1 gene provides a reliable and reproducible marker for Alzheimer disease is not credible because the regulation of transcription does not necessarily produce an analogous regulation of the protein levels or activities; protein activity can be regulated at multiple further levels: splicing, translation, intracellular localization, modulation by ligands, degradation/turnover, etc. the application does not provide any scientific evidence that the protein levels of ABCA1 are also reduced in the frontal cortex of patients, let alone the expression of "fragments" and "variants", or their activities.
- 2.3.2.2 The very different nature and etiology of the wide range of diseases under the label of "neurodegenerative" makes extremely unlikely, in the absence of experimental support, that a down-regulation of the ABCA1 mRNA can be considered a reliable and reproducible marker for all of them.
- 2.3.2.3 The fact that ABCA1 mRNA is down-regulated in post-mortem tissue of Alzheimer patients when comparing frontal vs. temporal cortex does not necessarily mean that said levels will be regulated in the same manner in the

body fluids of an Alzheimer patient when compared to a healthy person. First, the application does not provide any evidence that ABCA1 mRNA can be detected in body fluids or tissue samples which are suitable for prognosis, diagnosis, monitoring, etc. And second, if said mRNA could be detected, there is no evidence that it would be down-regulated when compared to the levels of a healthy person.

- 2.3.2.4 The fact that post-mortem tissue samples of Alzheimer patients show this differential mRNA expression does not imply that a person at risk of developing Alzheimer, but without any symptoms, will show the same effect, even if molecular analysis of his brain tissue was possible. There is no scientific evidence in the application in support of the prognostic methods.
- 2.3.3 Considering these facts, this IPEA has reasonable doubts concerning first, the reproducibility of the invention as claimed, and second, the burden of experimentation and inventive skill necessary to carry out the invention over the whole claimed area. Therefore, the present application cannot be considered sufficiently disclosed in the sense of Article 5 PCT. For the same reasons, and despite being formally supported by the description, the present claims cannot be considered supported in the sense of Article 6 EPC.